28 PRENATAL INTERACTION OF NICOTINE WITH DEVELOPING NERVOUS AND ENDOCRINE SYSTEMS

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Nicotine may affect the developing brain either through direct actions on developing nervous tissue or via effects on endocrine systems and metabolism. We focussed on developing central transmitter systems and neuroendocrine regulation of the Long Evans rat. Specific interactions of nicotine with developing neurons can be expected when nicotinic cholinergic receptor sites are formed. In vitro autoradiography reveals binding sites for (3H)nicotine in lower brainstem and spinal cord at gestational day (GD) 12, i.e., at the end of the embryonic period (Lichtensteiger et al., Progr. Brain Res. 73, 137, 1988). Later, they appear in anterior brain regions including cerebral cortex (GD 18). In cortex, a shift of maximum density from deep layers (VI) to layers IV+III occurs during the second and third postnatal week. As nicotinic receptor distribution changes throughout ontogeny and differs markedly from the adult condition, the effects of nicotine on a particular brain region may be quite different depending upon the developmental stage.

Effects of nicotine on nicotinic binding sites were studied in fetuses and offspring of time-pregnant rats implanted at GD 12 with osmotic minipumps delivering 0.25 mg/kg x hr during one week. At GD 21, quantitative autoradiography reveals a marked increase in density of (3H)nicotine binding sites in all brain areas studied, including substantia nigra, striatum and deep cortical layers. After delivery, receptor density returns to normal levels in most areas. However, in young adults (2 1/2 months), receptor density remains slightly elevated in cerebral cortex and has decreased to below control level in substantia nigra. The pattern in cortex and nigrostriatal system changes again until old age (20 months) which suggests differences in ageing processes.

Nicotinic receptors develop in close relation to pontine and mesencephalic catecholamine neuron groups of the fetus. Catecholamine metabolism of fetal forebrain is differently affected by acute and chronic nicotine administration (Ribary and Lichtensteiger, J. Pharmacol. Exp. Ther. 248, 786, 1989). Chronic prenatal exposure initiates a complex pattern of alterations in central dopamine and norepinephrine metabolism which changes from fetal through postnatal to adult life and differs between sexes. The pattern seen at PN 15 can tentatively be related to activity changes of male offspring (Schlumpf et al., Pharmacol. Biochem. Behav. 30, 199, 1988) in terms of the dopamine hypothesis of MBD.

Nicotine interferes with the organization of fetal neuroendocrine axes. In the male GD 18 rat fetus, it suppresses a characteristic rise in plasma testosterone and, moreover, increases corticosterone. This is followed by changes in the activity of brain steroid aromatase which converts androgens to estrogens and is important for sexual brain differentiation. Enzyme activity (measured by conversion of (3H)androstenedione) is reduced to female levels in male offspring at PN 5. This could impair organizing actions of androgens on the developing brain. In adult offspring, sexual dimorphism of saccharin preference is lost and male sexual behavior affected.

Thus, prenatal nicotine exposure initiates a complex interplay between effects on developing nervous and endocrine systems which continues after cessation of drug treatment.

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